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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,538	03/08/2000	Arlene A. Wise	S-91,714	2050

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	20

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/520,538	WISE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9-25* is/are pending in the application.

4a) Of the above claim(s) *9-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

[1] Claims 1 and 9-25 are pending in the application.

[2] Applicant's amendment to claim 1, cancellation of claim 8, and addition of claims 9-25 in Paper No. 17, filed 02/12/03, is acknowledged.

[3] Newly submitted claims 9-25 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the methods of claims 9-21 and 25 are independent from the method of claim 1 as the methods of claims 9-21 and 25 comprise different steps, utilize different products and yield different results. Also, the method of claim 1 can be used to make nucleic acids other than those of claim 22 and the nucleic acids of claim 22 can be made by a method other than that of claim 1 such as chemical synthesis and thus, claim 1 is distinct from the polynucleotides and host cell of claims 22-24.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 9-25 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

[4] Receipt of a supplemental Declaration in Paper No. 17 is acknowledged.

[5] Applicants' arguments in Paper No. 6 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 1 recites the limitation "the sensor domain" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim. It is suggested that, for example, applicant inserts "said DmpR protein comprising a sensor domain that detects phenols or substituted phenols" after "DmpR protein" in line 2. Such an amendment would correct antecedent basis and clarify the sensor domain as being part of the DmpR protein, which is not clear from the claim as written.

b) Claim 1 is confusing in the recitation of "removing the sensor domain from the DNA encoding the DmpR protein" in lines 5-6. It appears from the specification that *DNA encoding* the sensor domain is removed and the claim has been interpreted as such. It is suggested that applicants clarify the meaning of the claim by, for example, inserting "DNA encoding" before "the sensor domain" in lines 5-6 and inserting "DNA encoding the" before "sensor domain" in lines 6-7. Alternatively, if applicant does not amend the claim according to the examiner's suggestion, it is noted that there is insufficient antecedent basis for "the DNA encoding the DmpR protein" in line 6. In order to correct antecedent basis, it is suggested that, for example, applicant replaces "the DNA encoding the DmpR protein" with "a DNA encoding the DmpR protein".

Claim Rejections - 35 USC § 103

[8] Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pavel et al. (J Bacteriol 176:7550-7557) in view of Cadwell et al. ("Mutagenic PCR" pp 583-589 in "PCR Primer, A Laboratory Manual", Cold Spring Harbor Laboratory Press, 1995). Claim 1 is drawn to a method of enhancing a transcriptional activation of a reporter gene under the control of a promoter regulated by a DmpR protein in *Pseudomonas* or *Escherichia coli* bacteria in response to phenols and substituted phenols relative to transcriptional activation exhibited by wild-type bacteria of the same strain, said method comprising the steps of removing the DNA encoding the sensor domain, subjecting the sensor domain DNA to mutagenic PCR, ligating the mutant sensor domain into the DNA encoding the DmpR protein, and testing the bacteria for enhanced response to said phenols and substituted phenols.

Pavel et al. teach a method for generating a *Pseudomonas* DmpR effector specificity mutant by chemical mutagenesis of *Pseudomonas* DmpR-encoding DNA (page 7551, right column to page 7552, right column). Analysis of the resulting mutant revealed the presence of a single mutation in the DmpR sensor domain (referred to as the "A domain" by Pavel et al.) with no other mutation(s) present in either of the DmpR DNA binding or the transactivation domains (page 7552, left and right columns and page 7554, left column, bottom). Pavel et al. teach the DmpR sensor domain mutant exhibited increased transcriptional activation of a luciferase reporter gene under control of the *dmpR* promoter in response to the presence of 4-methylphenol, 3,4-dimethylphenol, and 4-ethylphenol relative to wild-type DmpR while maintaining a wild-type-like response to phenol, 2-methylphenol, and 3-methylphenol (page 7554, Figure 3). Because the DmpR sensor domain mutant and not the wild-type DmpR responds to 4-ethylphenol, Pavel et al. teach that the DmpR sensor domain mutant has thus gained the ability to recognize a novel effector compound (page 7556, left column, bottom). Pavel et al. teach that the application of microbial metabolic activities to detoxification and environmental cleanup has stimulated interest in the construction of strains with improved degradative efficiencies or expanded catabolic capacities and suggest two methods for genetically manipulating strains for improved efficiency: overexpression of catabolic enzymes and creation of effector specificity mutants (page 7555, right column and page 7556, left column). Pavel et al. teach that genetic manipulation to create effector specificity mutants is likely to be more successful in the construction of strains with improved degradative properties (page 7556, left column, top). The method of Pavel et al. does not include steps for mutating *only* the sensor domain of DmpR by PCR mutagenesis.

At the time of the invention, methods of randomly mutating DNA were well-known in the art. For example, Cadwell et al. teach a mutagenic PCR method of randomly mutating a nucleic acid in order to generate a library of mutant nucleic acids with scattered random mutations over the entire sequence (pages 583 and 584). Cadwell et al. further teach that after generating these mutants, one can apply a screening method to isolate individual clones that exhibit a particular property. (page 583).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Pavel et al. with Cadwell et al. to remove DNA encoding *only* the DmpR sensor domain, subject the sensor domain-encoding DNA to mutagenic PCR, and ligate the mutant sensor domain-encoding DNA into the DNA encoding DmpR. One would have been motivated to mutate *only* the sensor domain of DmpR because of the teachings of Pavel et al. who teaches mutation within the sensor domain alone (with no other mutations of the remaining domains of DmpR) results in an altered DmpR effector specificity and recognition of a novel effector compound for increased catabolic efficiency of phenolic compounds for detoxification and environmental cleanup. One would have been motivated to use mutagenic PCR to mutate the DmpR sensor domain in order to avoid the use of a DNA mutagen as used by Pavel et al. and because of the teachings of Cadwell et al. who taught that by using mutagenic PCR, one can create a library of mutants by random mutagenesis, thus increasing the number of potential mutations. One would have a reasonable expectation of success for removing DNA encoding *only* the DmpR sensor domain, subjecting the sensor domain-encoding DNA to mutagenic PCR, and ligating the mutant sensor domain-encoding DNA into the DNA encoding DmpR a method because of the results of Pavel et al. and Cadwell et al. Therefore, claim 1, drawn to the method described above, would have been obvious to one of ordinary skill in the art.

[9] Applicant argues none of the cited references comments as to the problems associated with targeting the DmpR sensor domain using random mutagenesis. Applicant argues that the cited references do not motivate one of ordinary skill in the art to use a targeted mutagenesis approach. Applicant's arguments are not found persuasive. It is noted that, prior to the work of Pavel et al., it was not known that effector compounds directly interacted with the sensor domain of DmpR (page 7556, left column, bottom). As Pavel et al. did not know prior to their results that the sensor domain was responsible for effector interaction, in order to create an effector specificity mutant, they applied a chemical mutagen to the entire DmpR coding sequence and therefore, their method was not targeted specifically to the sensor domain. After obtaining their results, Pavel et al. teach that "taken together, these data suggest that activation of DmpR and XylR is mediated by aromatic effector binding to the [sensor domains] of these

regulators" (page 7556, left column, bottom). Thus, with the evidence provided by Pavel et al., one of ordinary skill in the art would recognize that mutating the sensor domain alone will alter the effector specificity of DmpR. Pavel et al. teach that their objective was to identify an effector specificity mutant (page 7554, left column, middle), which resulted from mutation *only* within the sensor domain of DmpR – thus a skilled artisan would recognize that mutation of the sensor domain and no other domains would yield an effector specificity mutant that recognizes effector compounds not recognized by the wild-type DmpR. An ordinarily skilled artisan would recognize that in order to generate an effector specificity mutant without additional mutations within the transactivation and/or DNA binding domains of DmpR, one would remove DNA encoding only the sensor domain and subject only DNA encoding the DmpR sensor domain to mutagenic PCR in order to avoid use of a DNA mutagen.

Applicant argues (page 12, second paragraph of Paper No. 17) that the objective of Pavel et al. had nothing to do with the detection of organic pollutants. Applicant argues that given the purpose of Pavel et al., asserted by applicant to be studying the limitations of methylphenol catabolism, it is not surprising that the authors made no statement regarding targeted mutations of the DmpR sensor domain. Applicant's argument is not found persuasive. The objectives of Pavel et al. were several-fold – it is clear that at least one of the objectives of Pavel et al. is to broaden the effector specificity of DmpR for substituted phenols – achieved by chemical mutagenesis of the DmpR sensor domain. While the overall objective of Pavel et al. may not have been detection of organic pollutants, the results shown in Figure 3 (page 7554) demonstrate that Pavel et al. use a bacteria expressing the DmpR sensor domain mutant to compare the mutant and wild-type in their ability to detect phenol and substituted phenol via luciferase expression. It is noted that applicant acknowledges that phenolics *are* detected by Pavel et al. by stating, "the phenolics detected by Pavel's DmpR-E135K mutant" (page 13, line 4-5 of Paper No. 17). Furthermore, it is noted that the intended use of the claimed method, i.e., for detection of organic pollutants, is not a limitation of the claim and, even if this limitation were provided in the claim, the claimed method does not result in a manipulative difference as compared to the method made obvious

by the cited references and thus, the cited references would render obvious the claimed invention. See MPEP 2111.02 regarding intended use.

Applicant argues (page 13, first full paragraph of Paper No. 17) the phenolics detected by the DmpR sensor domain mutant of Pavel et al. are not those listed as EPA priority pollutants. Applicant's arguments are not found persuasive. Claim 1 is not so limited to a method for enhancing transcriptional activation of a reporter gene in response to *EPA priority pollutant* phenols and substituted phenols. Nowhere does claim 1 recite a limitation addressing EPA priority pollutant phenols. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Applicant argues (page 13, second full paragraph of Paper No. 17) with respect to the newly added claims, Pavel et al. provides no evidence that such mutants can be created. It is noted that the newly added claims have been withdrawn as these claims are drawn to non-elected inventions. See item 3 above. Therefore, applicant's argument addressing the newly added claims is moot.

Applicant argues there is no clear suggestion in Pavel et al. to mutate only the sensor domain and one of ordinary skill in the art would not have been led to combine Pavel et al. with Cadwell et al. Applicant's arguments are not found persuasive. As stated above, one of the objectives of Pavel et al. was to identify an effector specificity mutant (page 7554, left column, middle), which resulted from mutation *only* within the sensor domain of DmpR. A skilled artisan would clearly recognize there is no need to mutate other domains of DmpR, such as the DNA binding and transactivation domains, in order to generate an effector specificity mutant as Pavel et al. teach it is the sensor domain that interacts directly with the effector compound (page 7556, left column, bottom). Therefore, one of ordinary skill in the art, with an objective of creating effector specificity mutants, would recognize that one need only to mutate the sensor domain using mutagenic PCR.

Applicant argues (page 13, last paragraph of Paper No. 17) that they cannot identify any teachings in Pavel et al. that would provide an ordinarily skilled artisan with an expectation of success for enhanced recognition of any particular phenolic effector using the method of Pavel et al. Applicant argues that combining Pavel et al. and Cadwell et al. does not reach the legal threshold of a reasonable

expectation of success as the combination allegedly does not provide an indication or suggestion that applicant's method would result in DmpR mutants having such high level effector recognition properties. Applicant's argument is not found persuasive. It is noted that there is no limitation provided in the method of claim 1 to obtain a desired DmpR with enhanced recognition of a *particular* phenolic effector compound. Instead, the method applies to all phenolics and substituted phenolics, which one of ordinary skill in the art would not interpret as being a *specific* phenolic effector compound. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Applicant argues (page 14, first and second full paragraphs of Paper No. 17) that combining the references of Pavel et al. and Cadwell et al. with Willardson et al. and Minshull et al. would appear to add very little or could have assisted one of ordinary skill in the art. Applicant argues there is no teaching in Willardson et al. that would provide one of ordinary skill in the art with a reasonable expectation of success in making the claimed invention. Applicant argues that Minshull et al. may well have taught away from the claimed invention and assert that Minshull does not provide an example of mutating only a sensor domain, and thus Minshull does not provide one of ordinary skill in the art with a reasonable expectation of success in making the claimed invention. Applicant's arguments are not found persuasive. As the examiner has applied a rejection under 35 USC 103(a) using only the references of Pavel et al. and Cadwell et al. due to applicant's amendment of claim 1, applicant's arguments addressing the references of Willardson et al. and Minshull et al. are rendered moot as these references are no longer used in a rejection of claim 1.

Conclusion

[10] Claims 1 and 9-25 are pending.

[11] Claim 1 is rejected and is not in condition for allowance.

[12] Claims 9-25 are withdrawn from consideration.

Applicant's amendment necessitated rewriting the rejection under 35 USC 103(a) to remove the references of Willardson et al. and Minshull et al. The claim no longer recites XylR, thus the reference of Willardson et al., who taught the use of XylR in a biosensor, has been removed. Removal of Willardson et

al. also prompted removal of the reference of Minshull et al., who taught mutagenesis for use in altering specificity of biosensors. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit 1652

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